

TO THE ACADEMIC COUNCIL OF THE UNIVERSITY OF BELGRADE - FACULTY OF CHEMISTRY,

At the regular meeting of the Academic Council of the University of Belgrade - Faculty of Chemistry held on 18.01.2018. we have been chosen as the Committee members for review, evaluation and defense of the doctoral dissertation of Stepan M. Stepanović, MSc. in chemistry, research associate of the Center for Chemistry, Institute of Chemistry, Technology and Metallurgy, University of Belgrade, titled:

"Density functional approximations for spin state energetics in transition-metal complexes"

**„Aproksimacije funkcionala gustine u proučavanju energija spinskih stanja kompleksa
prelaznih metala“**

After reviewing the doctoral dissertation of the candidate, Stepan M. Stepanović, we submit to the Academic Council of the University of Belgrade - Faculty of Chemistry, the following:

R E P O R T

A. Preview of the doctoral dissertation content:

The doctoral dissertation of the candidate, Stepan M. Stepanović, with the title stated above, is written on 118 pages, A4 (1.5 line spacing) with 32 figures and 26 tables. The doctoral dissertation is written in English and contains the following chapters: *Introduction* (2 pages); a general part divided into two chapters: *Spin States in Chemistry* (11 pages) and *Theoretical and Methodological Background* (28 pages); results and discussion given in one chapter: *Our calculations* (69 pages), followed by a *General Conclusion* and list of

References. In addition, the doctoral dissertation contains Acknowledgements, Summary in the English and Serbian languages, a Contents list and a Biography of the author in the English and Serbian languages and ethical statement according to the University of Belgrade regulative.

In the **Introduction part**, the importance of spin states in transition metal chemistry is highlighted; the choice of methods is described and the general ideas and aims of the dissertation are presented.

The **General part** includes two sections. In the first section of the **General part**, the candidate gives a detailed description of spin states. Many of the phenomena and trends that are manifest in the first row transition metal series can be explained using simple qualitative considerations, such as “counting” Coulomb and exchange interactions. In the second section of the **General part**, theoretical aspects of wavefunction based methods, followed by the complementary Density Functional Theory (DFT) approach, are discussed. The foundations of the Hartree-Fock method, its limitations and source of the errors are elaborated. Following a short summary of post Hartree-Fock methods, Density Functional Theory is discussed in further detail culminating in a discussion of the appropriateness of Density Functional Approximations (DFAs) for the calculation of spin state energetics, which is the core concern of this thesis.

Results and discussion are reported in a single chapter, which is subdivided into four sections. The first section provides the systematic validation of the new S12g DFA, for the spin state energetics of nine iron complexes that show experimentally a diverse range of spin ground states and are representative of compounds biomimetic of P450cam and related active sites. The study of these challenging systems provided deeper insight into the performance of the S12g functional, compared with the established OPBE level of theory. The second sub-section of the **Results and discussion** is devoted to a systematic analysis of the effect of spin state and the ligand charge on the coordination chemistry of Mn^{II} , $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$, Co^{II} , Ni^{II} , Cu^{II} and Zn^{II} complexes of the 2,6-diacetylpyridinebis(semioxamazine) ligand and its mono- and di-anionic analogues. Complexes of polydentate acylhydrazone ligands with d-metals are particularly interesting since they have structural features that, potentially, lead to a remarkably diverse range of applications. The penultimate sub-section of the **Results and discussion** gives the analysis and rationalisation of spin state energetics in polypyrazolylborato complexes of first-row transition metals. The exploration of the effects

of substitution at position 3 and 5 of the pyrazolyl rings, as well as the influence of Jahn-Teller distortion on spin state switching, delivers deeper insight into the chemistry of these important enzyme mimics and spin crossover (SCO) compounds. In the final section of the **Results and discussion**, the mechanism of the catalytic cycle for catechol dioxygenase mimics is clarified utilizing density functional approximations (DFAs) that showed optimum performance in the earlier studies. The selected model systems are analysed in detail, with specific emphasis on their properties: similar biomimetic compounds can give different products, and there are many intermediates with complex electronic structure and close lying spin states in the catalytic cycle.

In the **General conclusion**, the candidate summarizes the results obtained by calculations of the spin states energetics, an analysis of the trends obtained, and provides suitable computational recipes for accurate determination of geometries, spin states and all related properties of the TM compounds studied.

The section **References** (218 citations) includes classical and the latest scientific papers in the field of spin states, DFT and (bio)inorganic chemistry related to this dissertation.

B. A brief description of the achieved results:

Within this doctoral thesis the spin states energetics were studied for selected sets of, both theoretically and experimentally, challenging and question raising transition metal complexes by means of DFT methods. The primary challenge is to establish a suitable level of theory, explanation of interrelationships between the structural properties and metal environment with the electronic structure, and rationalization of the results obtained, as well as, experimental findings.

The study of the influence of the geometrical parameters and implicit environment in the analysis of the challenging iron complexes and cytochrome p450 model systems, revealed S12g as an excellent level of theory for both structural parameters and electronic structure of these transition metal systems. The results give new insights into the application of the methods used in the exploration of (bio)inorganic reaction mechanisms. The most often used DFA, B3LYP, is clearly inadequate, favouring the high spin state always, in line with most of the hybrid DFAs. As an additional conclusion, attention is brought to errors in combining gas phase and COSMO approaches in geometry optimization and single point calculations.

The analysis of the influence of the spin state and the ligand charge on coordination preferences of Mn^{II} , $\text{Fe}^{\text{II}}/\text{Fe}^{\text{III}}$, Co^{II} , Ni^{II} , Cu^{II} and Zn^{II} for the 2,6-diacetylpyridine-bis(semioxamazide) ligand and its mono- and di-anionic analogues was performed by the means of DFT. All geometries are optimized with LDA which is known to provide good structural parameters for transition metal compounds and OPBE and S12g DFA are utilized for subsequent single point calculations. Although changes in spin states are, most often, followed by elongation of metal–ligand distances (due to occupation of antibonding orbitals in higher spin states), no difference in the mode of coordination was so far observed. For all protonation forms of dapsox ligand with metal in the high spin state, DFT calculations revealed the PBPY-7 geometry as the most stable one, regardless of the nature of metal/oxidation state (except for Ni^{II}), in accordance with experimental findings. However, lower spin states led to a change of coordination mode, i.e. octahedral complexes become the most stable one. To the best of our knowledge this was the first example where changing the spin state leads to a different coordination number. The experimentally observed inability of Ni^{II} to form heptacoordinate complexes with the dapsox ligand was rationalized in the same line of reasoning, as a simple consequence of the occupation of antibonding orbitals. The other coordination modes were also analysed.

The spin state ordering in polypyrazolylborato complexes of first-row transition metals are analysed and explained using OPBE for geometry optimizations (an example where it outperforms LDA systematically) and OPBE, SSB-D and S12g DFAs for spin state energetics. The results were in excellent agreement with the experimental data, both structurally and electronically (all spin state corroborate the experimental results). Furthermore, effects of substitution at the 3 and 5 position of pyrazolyl rings, as well as the influence of the Jahn-Teller distortion on spin state switching, were explored. The obtained results are rationalized on the basis of steric and electronic effects, and bring us one step further to the ultimate goal: achieving explicit control of spin states of transition metal compounds through rational design of ligand coordination.

These validation studies reveal that S12g is the optimum DFA, and hence it was used in the study of the mechanism of the catalytic cycle for catechol dioxygenase mimics. Full details of the catalytic cycle, with all accessible spin states and both possible pathways, intradiol and extradiol, have been explored. The model systems were selected not only because of their significance, but also due to their intriguing properties: similar biomimetic molecules give different products, and the abundance of short lived species with complicated

electronic structure and close lying spin states in the catalytic cycle. The selectivity was attributed to the breaking of a hydrogen bond (in one of the structures) along the branching point of the catalytic mechanism. The results and rationalizations provided will assist in the design of more selective catechol dioxygenation biomimetics.

The results given in this doctoral dissertation indicate that, in addition to experimental techniques, quantum chemical methods based on DFT play an important role in the analysis of transition metal compounds.

C. The comparative analysis of the candidate's results with the results from the literature:

Spin states play an important role in enzymatic reactions, in metal-oxo complexes, in spin crossover compounds and there exists even spin-state catalysis where (with one and the same compound) different reactions take place for different spin states. The close lying electronic states of various multiplicities influence the various properties of the transition metal complexes, e.g. both ground state properties and reactivity. However determining the correct spin ground state is a challenging task both from experimental and theoretical point of view.

Density Functional Theory (DFT) has become the preferred theoretical method for complicated electronic structure of coordination compounds, mainly because it provides a good compromise between the computational cost and accuracy. The challenge in application of DFT for spin states was first noted in 2001 (**H. Paulsen, L. Duelund, H. Winkler, H. Toftlund, A. X. Trautwein**, *Inorg. Chem.*, **2001**, *40* (9), pp 2201–2203), and it was concluded that early Generalized Gradient Approximation (GGA) DFAs favoured low-spin states, while hybrid functionals favoured high-spin states. Since then, many DFAs showed partial success, but mainly failures in the attempts to tackle the problem of close lying spin states in TM complexes (**Shengfa Ye and Frank Neese**, *Inorg. Chem.*, **2010**, *49* (3), pp 772–774; **Harvey J.N.** (2004) DFT Computation of Relative Spin-State Energetics of Transition Metal Compounds. In: Principles and Applications of Density Functional Theory in Inorganic Chemistry I. Structure and Bonding, vol 112. Springer, Berlin, Heidelberg; **Benjamin J. Houghton, Robert J. Deeth**, *Eur. J. Inorg. Chem.*, 2014: 4573–4580; **M. Reiher, O. Salomon and Artur B. Hess**, *Theor. Chem. Acc.: Theory, Comput. Model. (Theoretica Chimica Acta)*, **107**(1), 48–55 (2001); **Christopher J. Cramer and Donald G. Truhlar**,

Phys. Chem. Chem. Phys., 2009, **11**, 10757-10816; and many others) In 2004, the combination of a relatively new exchange functional, OPTX, with the PBE correlation part gave excellent results for the spin states of iron complexes, and hence a new DFA was born: OPBE (M. Swart, A. W. Ehlers and K. Lammertsma, *Mol.Phys.* **102**(23–24), 2467–2474 **2004**). Since OPBE showed very good performance of for spin states, and later as well S_N2 reaction barriers, it was mixed with PBE that gives good results for weak interactions. After incorporation of Grimme's D₂ dispersion energy, the SSB-D functional was created (M. Swart, M. Sola and F. M. Bickelhaupt, *J. Chem. Phys.* **131**(9), 094103 **2009**). Future refinement to make it numerically more stable and inclusion of Grimme's D₃ dispersion energy, led to its successor S12g (M. Swart, *Chem. Phys. Lett.* **580**, 166–171 **2013**).

Currently, there exists the situation that other research groups recommend the use of different density functionals for studying spin-state splitting. Hence, the design and benchmarking of DFAs for the accurate calculation of spin state energetics is of the utmost importance, and this area of research is still wide open and dynamic.

All the results presented in this thesis are in accordance with experimental and/or high level *ab initio* results.

D. Scientific papers published in the international journals and conference proceedings that are part of the doctoral dissertation:

M21a – Papers published in the top 10% of international journals

1. **Stepanović, S.**, Andjelković, L., Zlatar, M., Andjelković, K., Gruden-Pavlović, M., Swart, M. Role of spin state and ligand charge in coordination patterns in complexes of 2,6-diacetylpyridinebis(semioxamazide) with 3d-block metal ions: A density functional theory study (**2013**) *Inorganic Chemistry*, 52 (23), pp. 13415-13423. DOI: 10.1021/ic401752n, <http://pubs.acs.org/doi/10.1021/ic401752n>

M21 – Papers published in the top 30% of international journals

2. **Stepanović, S.**, Angelone, D., Gruden, M., Swart, M. The role of spin states in the catalytic mechanism of the intra- and extradiol cleavage of catechols by O₂. (2017) *Organic & Biomolecular Chemistry*, 15, 7860-7868, <http://dx.doi.org/10.1039/c7ob01814b>
3. Gruden-Pavlović, M., **Stepanović, S.**, Perić, M., Güell, M., Swart, M. A density functional study of the spin state energetics of polypyrazolylborato complexes of first-row transition metals (2014) *Physical Chemistry Chemical Physics*, 16 (28), pp. 14514-14522, <http://dx.doi.org/10.1039/C3CP55488K>

M23 - Paper published in the international journal

4. Gruden, M., **Stepanovic, S.**, Swart, M. Spin state relaxation of iron complexes: The case for OPBE and S12g (2015) *Journal of the Serbian Chemical Society*, 80 (11), pp. 1399-1410, <http://www.doiserbia.nb.rs/img/doi/0352-5139/2015/0352-51391500068G.pdf>

M34 - Papers published in the international conference proceedings as abstracts

1. **Stepanovic S.**, Nikolic A., Zivkovic A., Vlahovic F., Zlatar M., Kuraica M., The role of spin states in catalytic mechanism of the intra- and extradiol cleavage of catechols by O₂, 24th Congress of Chemists and Technologists of Macedonia with international participation, September 2016, Ohrid, Macedonia, oral presentation, Book of abstracts page 184, EN034.
2. **Stepanovic S.**, Gruden M., Swart M., The role of spin states in catalytic mechanism of the intra- and extradiol cleavage of catechols by O₂, ECOSTBio fifth Scientific workshop, September 2016, Krakow, Poland, Book of abstracts, page 52, poster P19.
3. **Stepanović S.**, Gruden M., Swart M., The role of spin states in catalytic mechanism of the intra- and extradiol cleavage of catechols by O₂, CM1305 ECOSTBio Summer School July 2016, Groningen, Netherlands, Book of abstracts pp 30.

4. **Stepanović S.**, Perić M., Gruden-Pavlović M., Swart M., Density functional study of spin state preferences in substituted polypyrazolylborato transition metal complexes, CM1305 ECOSTBio Summer School, July 2015, Groningen, Netherlands, Book of abstracts pp 30.
5. **Stepanović S.**, Perić M., Gruden-Pavlović M., Density functional study of spin state preferences in substituted polypyrazolylborato transition metal complexes, 50th Symposium on theoretical Chemistry: Quantum Chemistry and Chemical Dynamics, 14-18.09.2014, Vienna, Austria, Book of Abstracts P67

M64 - Papers published in the national conference proceedings as abstracts

1. Stepanović S., Gruden M., Swart M., The role of spin states in catalytic mechanism of the intra- and extradiol cleavage of catechols by O₂, Third conference of young chemists of Serbia, October 2016, Belgrade, Serbia, Book of abstracts page TH P02.

E. Conclusion (explanation of the scientific contribution of the doctoral dissertation):

In the submitted doctoral dissertation, the candidate, Stepan M. Stepanović, MSc. in Chemistry, studied the spin state energetics and its consequences for the structure, properties and catalytic behaviour of transition metal systems using DFT methods. A detailed analysis and reliable description of the spin state energetics rationalised key molecular properties, and the catalytic activity observed, and paves the way toward a better understanding of experimental findings in this field. The methods proposed, results obtained and their rationalization, provide direction towards explicit control of spin states of TM compounds and the rational design of TM compounds with desired properties.

We conclude that the presented scientific investigations are commensurate with contemporary trends in the field of general and inorganic (theoretical) chemistry and provide suitable computational recipes for accurate determination of geometries, spin states and essential related properties. Furthermore, understanding the connection between spin state and structure, properties and reactivity of a diverse class of transition-metal complexes, makes an important fundamental contribution.

The results of this doctoral dissertation are presented in 4 scientific papers (1 paper in the journal of M21a category, 2 papers in the journals of M21 category 1 paper in the journal of M23 category), among which the candidate is the first author on 2 papers, and 6 presentations at national and international conferences. Therefore, we propose to the Academic Council of the University of Belgrade-Faculty of Chemistry to accept the submitted doctoral dissertation of Stepan M. Stepanović, MSc. in Chemistry and approve its defence.

Belgrade,
02.02.2018.

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